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Prenatal Exposure to Nonpersistent Endocrine Disruptors and Behavior in Boys at 3 and 5 Years

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Background: Sex-specific associations have been reported between phthalates, bisphenol A (BPA), and child behavior. No data on large study populations are available for other phenols with possible endocrine-disrupting properties.

Objectives: We aimed to study associations between prenatal exposure to phthalates and several phenols on behavior among male infants.

Methods: We quantified 11 phthalate metabolites and nine phenols (four parabens, benzophenone-3, BPA, two dichlorophenols, triclosan) in spot urine samples collected during pregnancy among EDEN cohort mothers who delivered a boy. Mothers completed the Strength and Difficulties Questionnaire (SDQ) when their children were 3.1 ($n = 529$) and 5.6 ($n = 464$) y old.

Results: BPA was positively associated with the relationship problems subscale at 3 y [incidence rate ratio (IRR): 1.11; 95% confidence interval (CI): 1.03, 1.20] and the hyperactivity–inattention subscale scores at 5 y (IRR: 1.08; 95% CI: 1.01, 1.14). Mono-*n*-butyl phthalate (MnBP) was positively associated with internalizing behavior, relationship problem, and emotional symptom scores at 3 y. Monobenzyl phthalate (MBzP) was positively associated with internalizing behavior and relationship problems scores at 3 y. After dichotomizing SDQ scores, triclosan tended to be positively associated with emotional symptom subscales at both 3 and 5 y.

Conclusions: The observed associations between BPA, MnBP, and behavior in boys are consistent with previous findings. Further health impact assessment studies based on dose–response functions corrected for exposure misclassification are required to quantify the public health burden possibly entailed by such associations. https://doi.org/10.1289/EHP1314

Introduction

Neurodevelopment is a complex process that starts in humans as early as the second gestational week with neurulation and continues through adolescence (Rice and Barone 2000). Neurogenesis, neuron proliferation, migration, and differentiation of cells of the nervous system as well as synaptogenesis happen during fetal and early postnatal life. Disruption of these processes might be deleterious for the nervous system and may lead to neurodevelopmental disorders later in life. Neurodevelopmental disorders, such as intellectual disability, attention deficit/hyperactivity disorders, learning disabilities, or autism spectrum disorders affect about 12% of children worldwide (National Institute of Health and Medical Research 2002). Most disorders are likely to be caused by a combination of genetic and environmental factors (Sandin et al. 2014; van Loo and Martens 2007).

Several environmental chemicals, such as lead, mercury, and polychlorinated biphenyls, have been identified as neurotoxic, while a wide range of less extensively studied chemicals, including phenols and phthalates, are also suspected to affect child neurodevelopment (Grandjean and Landrigan 2006). Phenols include bisphenol A (BPA), a component of polycarbonate plastics and epoxy resins used in many consumer products (e.g., digital media, construction glazing, some toys, medical devices, food packaging); triclosan, an antibacterial agent used in personal care products such as antibacterial soaps or toothpastes; benzophenone-3, an ultraviolet (UV) filter; dichlorophenols, metabolites of intermediates used in the production of several herbicides and insecticides; and parabens used as preservatives in cosmetics and food. Phthalates are also used in a wide range of products, including personal care products (e.g., cosmetics, fragrances, shampoos), food packaging, and indoor residential environments (e.g., polyvinyl chloride flooring and wall covering, vinyl tiles, and shower curtains) (Hauser and Calafat 2005; Philippat et al. 2015).

Phenols and phthalates can interact with pathways that are crucial for the development of the nervous system. Some of these chemicals can indeed disrupt hormonal pathways and calcium signaling [reviewed by Miodovnik et al. (2014) for phthalates and Mustieles et al. (2015) for BPA]. Most epidemiological studies that evaluated potential associations between early life exposure to phenols and behavioral outcomes in children focused on BPA and reported effects that were sex-specific (Braun et al. 2011; Casas et al. 2015; Evans et al. 2014; Harley et al. 2013; F Perera et al. 2012; Perera et al. 2016; Roen et al. 2015). *In vitro* studies suggested endocrine-disrupting properties for other phenols, such as parabens and triclosan. Estrogenic effects have been indeed reported for parabens (Golden et al. 2005), while triclosan has been suspected to affect thyroid hormone homeostasis (Wu et al. 2016). However, to our knowledge, no study has investigated the associations between these other phenols and child

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behavior. Regarding phthalates, most epidemiological studies reported increased behavioral problems with prenatal exposure to at least one phthalate (Engel et al. 2010; Kobrosly et al. 2014; Lien et al. 2015; Whyatt et al. 2012), with the exception of one study conducted in Spain (Gascon et al. 2015). However, the type of behavior (e.g., hyperactivity, conduct problems) and the phthalate implicated often varied across studies.

We aimed at studying the associations between prenatal exposure to several phenols and phthalates and behavior among boys at 3 and 5 y.

Population and Methods

Study Population

The study population consisted of a subsample of mother–son pairs from the EDEN (study of pre- and early postnatal determinants of the child's development and health) cohort that recruited pregnant women in the obstetric departments of Nancy and Poitiers University hospitals (France) between February 2003 and January 2006. Participating in the study was proposed to all women visiting the prenatal clinics of Nancy and Poitiers University hospitals before their 24th week of amenorrhea. Exclusion criteria included multiple pregnancies, known diabetes before pregnancy, French illiteracy, or planning to move out of the region within the next 3 y. More details on the cohort are available in previous paper (Heude et al. 2016).

Phenol and phthalate biomarker concentrations were assessed for the mother of 604 boys of the EDEN cohort in the framework of previous projects that aimed at studying associations with growth (Botton et al. 2016; Philippat et al. 2012, 2014) and male genital anomalies (Chevrier et al. 2012). Selection criteria for these previous projects were: being a boy, the mother having one urine sample available during pregnancy for biomarker assessment, and having data on growth during the pre- and postnatal period (up to 3 y). Because of limited funding, we focused on a single sex rather than on two equal-size groups of girls and boys. Among the 604 children included in these previous projects, 546 had data on behavior at 3 and/or 5 y and were included in the present study.

The EDEN cohort received approval from the ethics committee of Kremlin-Bicêtre University Hospital. The participants gave informed written consent for themselves and for their children to be included in the cohort.

Assessment of Child Behavior

Behavior was assessed at 3.1 [standard deviation (SD): 0.1] and 5.6 (SD: 0.2) y using the Strength and Difficulties Questionnaire (SDQ) completed by the mother (Goodman 1997). This questionnaire includes 25 items scored on a 3-point scale (0: not true; 1: somewhat true; 2: certainly true) that were combined into 4 difficulties subscores: conduct problems, hyperactivity–inattention, peer relationship problems, and emotional symptoms subscores, and one strength subscore: prosocial behavior. The score for each subscale ranged from 0 to 10. We then computed an externalizing (sum of the conduct problems and hyperactivity–inattention scores) and an internalizing behavior score (sum of the peer relationship problems and emotional symptoms scores). Score of the strength subscale was reversed prior to analysis so that for all SDQ subscales higher scores meant increased difficulties. Construct of each subscore is detailed in Table S1.

Exposure Assessment

Women were asked to collect first morning urine void at home just before the prenatal study visit. If forgotten, urine collection was done at the hospital during the prenatal visit. We quantified 9 phenols and 11 phthalate metabolites in maternal spot urine samples collected between 22 and 29 gestational wk using online solid phase extraction–high-performance liquid chromatography–isotope dilution tandem mass spectrometry at the Centers for Disease Control and Prevention (CDC) laboratory (Silva et al. 2007; Ye et al. 2005). Creatinine, a proxy of urine dilution, was also measured. The analysis of blinded urine specimens at CDC was determined not to constitute engagement in human subjects research. We used instrumental reading values for biomarker concentrations below the limits of detection. Instrumental reading values equal to 0 (i.e., indicative of no signal) were replaced by the lowest instrumental reading value divided by the square root of 2. We computed the total parabens and dichlorophenol concentrations by summing molar concentrations of the four parabens ($\sum$ parabens) and the two dichlorophenols ($\sum$ dichlorophenols), respectively. For phthalates, we computed the total di(2-ethylhexyl) phthalate (DEHP) metabolite concentration ($\sum$ DEHP) by summing molar concentrations of mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxy-hexyl) phthalate (MEHHP), mono(2-ethylhexyl) phthalate (MEHP), and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP).

Statistical Analysis

Biomarker concentrations were standardized for creatinine and sampling conditions (e.g., hour of sampling, gestational age at sampling) prior to analysis using a two-step standardization approach developed by our team (Mortamais et al. 2012; Philippat et al. 2014). This method consists of *a*) studying the associations between each biomarker concentration and sampling conditions and creatinine concentrations through adjusted linear regression modeling; and *b*) using the measured biomarker concentrations and the effects of sampling conditions and of creatinine estimated during step 1 to predict standardized concentrations that would have been observed if all samples had been collected under the same conditions. These standardized concentrations were used in all analyses.

We used adjusted negative binomial regressions to study the associations between each standardized biomarker concentration and each SDQ subscore. Biomarker concentrations were log–transformed (base 2) prior to analysis so that the incidence rate ratios (IRRs) corresponded to the multiplicative change in the probability of the SDQ scores increasing by one unit for a doubling in biomarker concentration.

Adjustment factors were selected based on *a priori* knowledge and included factors possibly related to both exposures and child behavior, or to child behavior only. These factors included child age at assessment, recruitment center (Poitiers vs. Nancy), maternal age (continuous), parity (0, 1, 2 or more children), maternal body mass index (continuous), parental education (average length of the mother and father's education), breastfeeding duration (never, $\leq$3 mo, >3 mo), household income [$\leq$€1,500; €1,500 to €3,000, $\geq$€3,000 (euros) per mo], smoking during pregnancy (yes/no), and maternal psychological difficulties during pregnancy (yes/no). The maternal psychological difficulties score was constructed by combining scores of the Center for Epidemiologic Studies Depression Scale Revised (CESD), a questionnaire designed to assess depression and scores of the State-Trait Anxiety Inventory (STAI) that evaluates anxiety. The CESD and the STAI were completed by the mother during pregnancy.

Sensitivity Analyses

Several sensitivity analyses were conducted. To explore to which extent associations could be confounded by exposure to other phenols

or phthalates, we ran analyses simultaneously adjusted for all phenols (BPA, benzophenone-3, triclosan, $\sum$dichlorophenols, $\sum$parabens), and phthalate metabolites [monoethyl phthalate (MEP), mono-*n*-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), monocarboxyoctyl phthalate (MCOP), mono(3-carboxypropyl) phthalate (MCPP), monocarboxynonyl phthalate (MCNP), and $\sum$DEHP] concentrations.

Benzophenone-3 is used as a UV filter in sunscreens. Use of sunscreens is likely to vary across seasons. Because season of birth has been associated with increased risks of neurodevelopmental disorders such as autism spectrum disorders and schizophrenia (Torrey et al. 1997), we performed an additional analysis in which models that looked at the associations between benzophenone-3 and SDQ scores were additionally adjusted for season of urine collection.

We also dichotomized the SDQ scores at the 85th percentile (Melchior et al. 2015) and used adjusted logistic regression models to study the associations of these binary outcomes with biomarker concentrations.

Finally, as an attempt to take into account the effect of measurement error resulting from the use of a spot urine sample to assess exposure, we reported in the supplemental material the effect estimates corrected for exposure misclassification using the following formula (Rappaport et al. 1995):

$$\widehat{\beta}_{jcorr} = \frac{\widehat{\beta}_{jobs}}{\widehat{ICC}_j}$$

where $\widehat{\beta}_{jobs}$ is the estimated association from our main analysis between a biomarker j and an SDQ score, $\widehat{\beta}_{jcorr}$ our corrected estimate, and ICC_j the intraclass correlation coefficient for the biomarker j considered. A simulation study has shown that this *a posteriori* disattenuation approach led to unbiased effect estimates in the presence of exposure measurement error of classical type (Perrier et al. 2016). We had only one urine sample per participant in our cohort and were not able to compute ICCs from our data. For this reason, we used ICCs from previous studies among pregnant women. ICCs were 0.1 for MCNP; 0.2 for BPA, $\sum$DEHP, and MCPP; 0.3 for MCOP; 0.4 for MnBP, MBzP, MEP, and MiBP; and 0.6 for $\sum$dichlorophenols, $\sum$parabens, benzophenone-3, and triclosan (Cantonwine et al. 2014; Philippat et al. 2013).

Given the relatively limited evidence regarding possible effects of phenols and phthalates on child neurodevelopment and the breadth of data available in our cohort, we chose to adopt an exploratory approach and reported in the results section all associations (p-values <0.05 and p-values between 0.05 and 0.1). In a sensitivity analysis, we accounted for multiple comparisons by applying a false discovery rate (FDR) correction (Benjamini and Hochberg 1995).

Analyses were performed using Stata/SE 14.1 (StataCorp LLC).

Results

Characteristics of the study population are presented in Table 1. Parents tended to be highly educated: 57% of the mothers and 47% of the fathers had 2 or more y of education after high school; 28% of the mothers reported having psychological difficulties during pregnancy, and 27% reported having never breastfed their child. Spearman correlation coefficients between the SDQ scores at 3 y and at 5 y were below 0.5 for the emotional, peer relationship problem, and prosocial scores, and ranged from 0.51 to 0.66 for the three other scores (Table S2). Phenols were detected in 73% (triclosan) to 100% (BPA; 2,5-dichlorophenols; methylparaben) of maternal urine samples, while all phthalate metabolites were detected in more than 97% of the samples (Table S3). We observed moderate to high Spearman correlation coefficients (rho) between the two dichlorophenols (rho = 0.69), the four parabens (rho ≥0.48), the four DEHP metabolites (rho ≥0.78), and between MNBP and MCPP (rho = 0.62). The remaining correlation coefficients were below 0.43 (Table S4).

Table 1. Characteristics of our study population ($n = 546$[a] mother–son pairs of the French EDEN mother–child cohort).

Characteristics	*n* (%)
Recruitment center	
Poitiers	323 (59)
Nancy	223 (41)
Parity	
Nulliparous	255 (47)
≥1	290 (53)
Missing	1 (0)
Maternal education	
≤2 y after high school	226 (41)
High school +2 y	127 (23)
High school +3 y	186 (34)
Missing	7 (1)
Paternal education	
≤2 y after high school	257 (47)
High school +2 y	118 (22)
High school +3 y	137 (25)
Missing	34 (6)
Household monthly income (euros)	
≤1,500	70 (13)
1,500–3,000	328 (60)
≥3,000	146 (27)
Missing	2 (0)
Smoking during pregnancy	
No	419 (76)
Yes	125 (23)
Missing	2 (0)
Maternal psychological difficulties[b]	
No	394 (72)
Yes	152 (28)
Breastfeeding duration	
Never	145 (27)
≤3 mo	221 (40)
3 mo	180 (33)
	Mean (SD)
Maternal age at pregnancy	29.7 (4.7)
Body mass index (kg/m^2)	23.2 (4.5)

Note: SD, standard deviation; SDQ, Strength and Difficulties Questionnaire.
[a]Includes mother–son pairs that have biomarker assessments and SDQ scores at 3 or 5 years.
[b]Maternal depression and/or maternal anxiety during pregnancy.

Phenols and Child Behavior

Maternal BPA was associated with the internalizing behavior score [IRR for a doubling in concentration: 1.06; 95% confidence interval (CI): 1.00, 1.12] and the peer relations problem (IRR: 1.11; 95% CI: 1.03; 1.20) score at 3 y. BPA was also associated with the externalizing behavior score (IRR: 1.05; 95% CI: 1.00, 1.11) and the hyperactivity–inattention score (IRR: 1.08; 95% CI, 1.01; 1.14) at 5 y (Tables 2 and 3).

Triclosan tended to be positively associated with several SDQ scores at 3 y with IRRs closer to 1 than those observed for BPA: IRR of 1.01 (95% CI: 1.00, 1.03), 1.02 (95% CI: 1.00, 1.04), and 1.01 (95% CI: 1.00; 1.03) for the externalizing, emotional symptoms, and conduct problem scores at 3 y, respectively (Table 2).

No other phenol was associated with the internalizing and externalizing scores at 3 or 5 y (p-values >0.14, Tables 2, 3). However, when we looked at each SDQ subscore separately, scores of the conduct problems subscale at 5 y tended to increase

Table 2. Adjusted associations between phenols, phthalate metabolites and behavior at 3 y among boys of the EDEN mother–child cohort ($n = 518$ to 520 mother–son pairs, depending of the subscale).

	Emotional symptoms		Conduct problems		Peer relationship problems		Hyperactivity–inattention problems		Prosocial behavior		Externalizing behavior		Internalizing behavior	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Phenols														
∑ Dichlorophenols	1.02	(0.98, 1.06)	1.01	(0.99, 1.04)	0.99	(0.95, 1.03)	1.00	(0.98, 1.03)	1.00	(0.98, 1.03)	1.01	(0.99, 1.03)	1.00	(0.97, 1.03)
Bisphenol A	1.01	(0.94, 1.09)	1.03	(0.98, 1.08)	1.11	(1.03, 1.20)**	1.04	(0.99, 1.08)	1.05	(0.99, 1.10)	1.03	(0.99, 1.07)	1.06	(1.00, 1.12)*
Benzophenone-3	1.00	(0.96, 1.03)	0.99	(0.97, 1.01)	1.01	(0.98, 1.05)	1.01	(0.99, 1.03)	0.99	(0.96, 1.01)	1.00	(0.98, 1.02)	1.00	(0.98, 1.03)
Triclosan	1.02	(1.00, 1.04)*	1.01	(1.00, 1.03)*	1.00	(0.98, 1.03)	1.01	(1.00, 1.03)	1.01	(0.99, 1.03)	1.01	(1.00, 1.03)*	1.01	(0.99, 1.03)
∑ Parabens	1.00	(0.97, 1.04)	0.99	(0.97, 1.02)	0.99	(0.95, 1.02)	0.98	(0.96, 1.00)	0.97	(0.94, 1.00)**	0.99	(0.97, 1.01)	1.00	(0.97, 1.03)
Phthalates														
MEP	1.03	(0.97, 1.08)	1.00	(0.97, 1.04)	0.97	(0.92, 1.03)	1.00	(0.97, 1.03)	0.99	(0.95, 1.03)	1.00	(0.97, 1.03)	1.00	(0.96, 1.04)
MnBP	1.06	(1.00, 1.12)**	1.01	(0.97, 1.04)	1.06	(1.00, 1.12)**	0.99	(0.95, 1.02)	0.99	(0.95, 1.03)	1.00	(0.97, 1.03)	1.06	(1.01, 1.11)**
MiBP	0.97	(0.90, 1.05)	1.00	(0.96, 1.05)	1.05	(0.98, 1.13)	0.95	(0.91, 1.00)**	0.99	(0.94, 1.05)	0.97	(0.94, 1.01)	1.01	(0.95, 1.07)
MCPP	1.03	(0.96, 1.11)	0.98	(0.94, 1.03)	1.04	(0.97, 1.12)	0.96	(0.92, 1.00)*	0.95	(0.90, 1.00)*	0.97	(0.93, 1.01)	1.04	(0.98, 1.10)
MBzP	1.02	(0.96, 1.09)	1.00	(0.97, 1.04)	1.07	(1.01, 1.13)**	0.98	(0.94, 1.01)	0.97	(0.93, 1.02)	0.99	(0.96, 1.02)	1.04	(1.00, 1.09)*
MCOP	1.02	(0.95, 1.10)	1.01	(0.97, 1.06)	0.99	(0.92, 1.06)	0.98	(0.94, 1.03)	1.00	(0.95, 1.05)	1.00	(0.96, 1.04)	1.01	(0.95, 1.06)
MCNP	1.01	(0.95, 1.07)	0.99	(0.95, 1.03)	1.00	(0.94, 1.06)	0.97	(0.93, 1.01)	0.98	(0.94, 1.03)	0.98	(0.95, 1.01)	1.00	(0.95, 1.05)
∑ DEHP	1.04	(0.97, 1.11)	0.99	(0.95, 1.04)	1.05	(0.98, 1.12)	0.97	(0.93, 1.01)	0.99	(0.94, 1.04)	0.98	(0.94, 1.02)	1.04	(0.99, 1.10)

Note: CI, confidence interval; ∑DEHP, molecular sum of di(2-ethylhexyl) phthalate metabolites; ∑dichlorophenols, molecular sum of 2,4 and 2,5-dichlorophenols; IRR, incidence rate ratio; MBzP, monobenzyl phthalate; MCNP, monocarboxynonyl phthalate; MCOP, monocarboxyoctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MEP, monoethyl phthalate; MiBP. mono-isobutyl phthalate, MnBP, mono-*n*-butyl phthalate; ∑parabens, molecular sum of methyl, ethyl, propyl, and butyl parabens. Associations adjusted for recruitment center, maternal age, parity, parental education, breastfeeding duration, household income, smoking during pregnancy, maternal psychological difficulties during pregnancy, and child age at assessment. IRR are reported for a doubling in biomarkers concentrations.
*$p \leq 0.10$; **$p \leq 0.05$.

in association with ∑dichlorophenols (IRR: 1.03; 95% CI: 1.00, 1.07). Benzophenone-3 was associated with a decreased emotional symptom score at 5 y (IRR, 0.96; 95% CI: 0.93, 1.00), while ∑parabens were associated with increased prosocial behavior score at 3 y (IRR, 0.97; 95% CI: 0.94, 1.00) (Tables 2, 3).

Phthalates and Child Behavior

Several phthalate metabolites were associated with SDQ scores at 3 y (Table 2). MnBP was associated with internalizing (IRR: 1.06; 95% CI: 1.01, 1.11) as well as with the relationship problems (IRR: 1.06; 95% CI: 1.00, 1.12) and emotional problems (IRR: 1.06; 95% CI: 1.00; 1.12) scores at 3 y. MBzP was associated with increased internalizing (IRR: 1.04; 95% CI: 1.00, 1.09) and relationship problems scores (IRR: 1.07; 95% CI: 1.01, 1.13). Two phthalates were associated with lower SDQ scores: MiBP and MCPP concentrations were indeed associated with decreased hyperactivity–inattention scores [IRRs were 0.95 (95% CI: 0.91, 1.00) and 0.96 (95% CI: 0.92, 1.00) for MiBP and MCPP, respectively]. MCPP was also associated with decreased prosocial behavior scores (IRR: 0.95; 95% CI: 0.9; 1.0). None of the associations we observed between phthalate metabolites and SDQ scores at 3 y persisted at 5 y (Table 3).

Sensitivity Analyses

Studying SDQ scores as dichotomized variables overall led to similar results as studying them as count outcomes for BPA, MBzP, MnBP, and MCPP (Tables 4, 5). For triclosan, the positive association seen at 3 y with the emotional symptoms score persisted at 5 y when SDQ scores were dichotomized (Tables 4, 5). The inverse associations we observed between benzophenone-3 and emotional symptoms at 5 y, MiBP and hyperactivity–inattention at 3 y, and ∑parabens and prosocial behavior at 3 y were strongly attenuated when SDQ scores were dichotomized and did not remain significant. Odds ratios (ORs) were 0.93 (95% CI: 0.82, 1.05), 0.91 (95% CI: 0.72, 1.16), and 0.92 (95% CI: 0.80, 1.06) for benzophenone-3, MiBP, and ∑parabens, respectively (Tables 4, 5). Similarly, the association between ∑dichlorophenols and conduct problems at 5 y did not remain when this score was dichotomized (OR: 0.90; 95% CI: 0.80, 1.10, Table 5). Finally, a few associations emerged: ∑DEHP was associated with increased risk of emotional symptoms (OR: 1.27, 95% CI: 1.01, 1.60) and internalizing behavior (OR: 1.41; 95% CI: 1.13, 1.76) at 3 y, while MCNP was associated with decreased risk of hyperactivity–inattention at 3 y (OR: 0.72; 95% CI: 0.55, 0.93).

Adjustment for season did not change the association observed between benzophenone-3 and the emotional subscale. Running models simultaneously adjusted for all of the biomarkers measured in our study did not strongly affect our findings, and the effect estimates were close to those of the main analyses that consisted of studying each biomarker separately (Tables S5, S6).

As expected, IRRs and ORs corrected for exposure measurement error using the formula based on ICCs were larger (absolute values) than the uncorrected ones (Tables S7 to S10). As an example, after correction, OR was as high as 5.4 (95% CI: 1.45, 20.0) for the association between BPA, one of the chemicals with the highest variability, and the hyperactivity and inattention scores at 5 y (Table S10). OR without correction was 1.40 (95% CI: 1.0, 1.82, Table 5).

When we applied a correction for multiple comparisons using an FDR method, none of the associations reported in the results section remained significant, the lowest corrected *p*-value being 0.42 for the association between BPA and the peer relations problem score at 3 y.

Discussion

In our study of 546 women who delivered a boy, three phenols (BPA, triclosan, and ∑dichlorophenols) and two phthalates (MnBP, MBzP) biomarkers were positively associated with scores in one or more subscales of the SDQ, while inverse association was observed for other biomarkers (benzophenone-3, MiBP, MCPP). Most of the observed IRRs were close to 1. It should be kept in mind that a detailed assessment of the public health impact of these exposures would require a thorough health impact assessment, taking into account the distribution of

Table 3. Adjusted associations between phenols, phthalate metabolites and behavior at 5 y among boys of the EDEN mother–child cohort ($n = 457$ or 458 mother–son pairs, depending of the subscale).

	Emotional symptoms		Conduct problems		Peer relationship problems		Hyperactivity–inattention problems		Prosocial behavior		Externalizing behavior		Internalizing behavior	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Phenols														
∑ Dichlorophenols	1.00	(0.97, 1.04)	1.03	(1.00, 1.07)*	0.99	(0.94, 1.04)	1.01	(0.98, 1.04)	1.00	(0.96, 1.04)	1.02	(0.99, 1.05)	1.00	(0.97, 1.03)
Bisphenol A	1.03	(0.95, 1.11)	1.02	(0.95, 1.10)	1.02	(0.93, 1.13)	1.08	(1.01, 1.14)**	1.05	(0.96, 1.14)	1.05	(1.00, 1.11)**	1.03	(0.96, 1.10)
Benzophenone-3	0.96	(0.93, 1.00)**	1.00	(0.97, 1.04)	1.01	(0.97, 1.06)	1.02	(0.99, 1.04)	1.02	(0.98, 1.06)	1.01	(0.99, 1.04)	0.98	(0.95, 1.01)
Triclosan	1.01	(0.99, 1.03)	1.00	(0.98, 1.02)	1.01	(0.98, 1.04)	1.00	(0.98, 1.01)	0.99	(0.97, 1.02)	1.00	(0.98, 1.02)	1.01	(0.99, 1.03)
∑ Parabens	0.99	(0.95, 1.02)	0.99	(0.96, 1.03)	0.99	(0.94, 1.04)	0.98	(0.95, 1.00)	0.99	(0.95, 1.03)	0.98	(0.96, 1.01)	0.99	(0.96, 1.02)
Phthalates														
MEP	1.01	(0.95, 1.06)	1.03	(0.98, 1.08)	0.99	(0.92, 1.05)	0.99	(0.95, 1.03)	0.96	(0.91, 1.02)	1.01	(0.97, 1.05)	1.00	(0.95, 1.04)
MnBP	1.00	(0.94, 1.05)	1.02	(0.97, 1.07)	1.05	(0.99, 1.13)	1.01	(0.97, 1.05)	1.01	(0.95, 1.07)	1.01	(0.97, 1.06)	1.02	(0.97, 1.07)
MiBP	0.97	(0.90, 1.05)	1.01	(0.94, 1.08)	1.00	(0.91, 1.09)	0.97	(0.91, 1.02)	1.04	(0.96, 1.13)	0.98	(0.93, 1.04)	0.98	(0.92, 1.05)
MCPP	0.98	(0.91, 1.05)	1.04	(0.97, 1.11)	1.06	(0.97, 1.16)	1.01	(0.95, 1.07)	0.99	(0.91, 1.08)	1.02	(0.97, 1.08)	1.01	(0.95, 1.08)
MBzP	1.03	(0.97, 1.09)	0.98	(0.93, 1.04)	1.01	(0.94, 1.09)	1.00	(0.95, 1.04)	0.98	(0.92, 1.04)	0.99	(0.95, 1.03)	1.02	(0.97, 1.08)
MCOP	1.04	(0.97, 1.12)	1.00	(0.94, 1.06)	0.99	(0.91, 1.08)	1.01	(0.96, 1.07)	0.94	(0.87, 1.02)	1.01	(0.96, 1.06)	1.02	(0.96, 1.09)
MCNP	1.04	(0.98, 1.10)	0.99	(0.93, 1.04)	1.03	(0.96, 1.11)	0.99	(0.94, 1.04)	0.98	(0.92, 1.05)	0.99	(0.94, 1.03)	1.04	(0.98, 1.09)
∑ DEHP	1.01	(0.94, 1.08)	0.99	(0.93, 1.06)	1.03	(0.94, 1.12)	1.01	(0.96, 1.07)	0.97	(0.90, 1.05)	1.00	(0.95, 1.06)	1.02	(0.95, 1.08)

Note: CI, confidence interval; ∑DEHP, molecular sum of di(2-ethylhexyl) phthalate metabolites; ∑dichlorophenols, molecular sum of 2,4 and 2,5-dichlorophenols; IRR, incidence rate ratio; MBzP, monobenzyl phthalate; MCNP, monocarboxynonyl phthalate; MCOP, monocarboxyoctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-*n*-butyl phthalate; ∑parabens, molecular sum of methyl, ethyl, propyl, and butyl parabens. Associations adjusted for recruitment center, maternal age, parity, parental education, breastfeeding duration, household income, smoking status, maternal psychological difficulties during pregnancy, and child age at assessment. IRRs are reported for a doubling in biomarkers concentrations.
*$p \leq 0.10$; **$p \leq 0.05$.

exposure levels and dose–response functions, if possible, corrected for exposure misclassification. Our study is among the first to simultaneously consider a rather large number of biomarkers from the phthalates and phenols families in relation to several behavioral scales. Because we tested many associations, some of our results might be chance finding, as suggested by the fact that none of the observed *p*-values remained significant after FDR correction. For this reason, in the following discussion, we focused on the associations for which some consistency was observed with the previous human literature focusing on prenatal exposure, or with animal literature when no human study was available.

In our study population, BPA was associated with increased scores on the internalizing behavior and peer relationship problem subscales at 3 y and on the externalizing behavior and hyperactivity–inattention subscales at 5 y. Associations between prenatal BPA concentrations and internalizing and externalizing behavior scores in boys have been reported in most of the previous studies evaluating such behaviors (Evans et al. 2014; Harley et al. 2013; FP Perera et al. 2012; Roen et al. 2015) (Table S11). Regarding specific subscales, an increased score on the hyperactivity–inattention subscale in association with prenatal exposure to BPA has been previously reported among boys at 4, but not at 7 y (Casas et al. 2015). Other studies have reported opposite

Table 4. Adjusted associations between phenols, phthalate metabolites and dichotomized Strength and Difficulties Questionnaire (SDQ) scores at 3 y ($n = 518$ to 520 mother–son pairs, depending of the subscale).

	Emotional symptoms		Conduct problems		Peer relationship problems		Hyperactivity–inattention problems		Prosocial behavior		Externalizing behavior		Internalizing behavior	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Phenols														
∑ Dichlorophenols	1.06	(0.94, 1.20)	0.97	(0.83, 1.13)	0.99	(0.85, 1.14)	1.04	(0.92, 1.18)	1.02	(0.90, 1.17)	1.05	(0.93, 1.18)	1.04	(0.93, 1.18)
Bisphenol A	0.92	(0.70, 1.19)	1.08	(0.81, 1.43)	1.40	(1.07, 1.84)**	1.07	(0.83, 1.38)	1.07	(0.82, 1.39)	1.01	(0.79, 1.29)	1.22	(0.96, 1.55)*
Benzophenone-3	1.00	(0.89, 1.13)	1.02	(0.89, 1.16)	1.03	(0.91, 1.17)	1.01	(0.89, 1.13)	0.98	(0.86, 1.11)	0.98	(0.87, 1.10)	1.02	(0.91, 1.14)
Triclosan	1.07	(0.99, 1.17)*	1.10	(1.00, 1.21)**	1.06	(0.97, 1.16)	1.02	(0.94, 1.10)	1.07	(0.99, 1.17)*	1.05	(0.97, 1.13)	1.05	(0.97, 1.14)
Parabens	1.01	(0.89, 1.15)	1.00	(0.87, 1.16)	0.97	(0.84, 1.12)	1.01	(0.89, 1.15)	0.92	(0.80, 1.06)	0.94	(0.83, 1.07)	1.03	(0.92, 1.17)
Phthalates														
MEP	1.14	(0.95, 1.36)	0.95	(0.77, 1.17)	1.04	(0.86, 1.26)	1.07	(0.89, 1.29)	0.98	(0.81, 1.19)	1.00	(0.84, 1.20)	0.98	(0.83, 1.17)
MnBP	1.10	(0.91, 1.31)	0.99	(0.80, 1.22)	1.16	(0.95, 1.41)	0.95	(0.79, 1.16)	0.92	(0.75, 1.13)	0.93	(0.78, 1.12)	1.22	(1.03, 1.44)**
MiBP	0.87	(0.68, 1.12)	1.13	(0.86, 1.49)	1.16	(0.89, 1.53)	0.91	(0.72, 1.16)	1.10	(0.85, 1.43)	0.93	(0.74, 1.17)	1.09	(0.87, 1.38)
MCPP	1.02	(0.80, 1.31)	0.79	(0.59, 1.07)	1.13	(0.86, 1.47)	0.79	(0.61, 1.04)*	0.80	(0.61, 1.06)	0.82	(0.64, 1.05)	1.20	(0.95, 1.51)
MBzP	0.99	(0.81, 1.22)	0.99	(0.78, 1.25)	1.25	(1.00, 1.56)**	0.94	(0.76, 1.15)	0.94	(0.76, 1.17)	0.94	(0.78, 1.15)	1.19	(0.98, 1.44)
MCOP	1.02	(0.81, 1.30)	1.14	(0.89, 1.47)	1.04	(0.79, 1.35)	0.85	(0.66, 1.10)	0.98	(0.77, 1.25)	1.07	(0.86, 1.34)	1.08	(0.87, 1.35)
MCNP	0.90	(0.72, 1.14)	1.00	(0.78, 1.27)	1.09	(0.87, 1.36)	0.72	(0.55, 0.93)**	0.84	(0.65, 1.08)	0.85	(0.68, 1.07)	1.00	(0.81, 1.23)
∑ DEHP	1.27	(1.01, 1.60)**	1.10	(0.85, 1.43)	1.09	(0.84, 1.41)	1.03	(0.81, 1.30)	1.18	(0.94, 1.50)	1.07	(0.85, 1.34)	1.41	(1.13, 1.76)*

Note: CI, confidence interval; ∑DEHP, molecular sum of di(2-ethylhexyl) phthalate metabolites; ∑dichlorophenols, molecular sum of 2,4 and 2,5-dichlorophenols; MBzP, monobenzyl phthalate; MCNP, monocarboxynonyl phthalate; MCOP, monocarboxyoctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-*n*-butyl phthalate; OR, odds ratio; ∑parabens, molecular sum of methyl, ethyl, propyl, and butyl parabens. Associations adjusted for recruitment center, maternal age, parity, parental education, breastfeeding duration, household income, smoking status, maternal psychological difficulties during pregnancy, and child age at assessment. IRRs are reported for a doubling in biomarkers concentrations.
*$p \leq 0.10$; **$p \leq 0.05$.

Table 5. Adjusted associations between phenols, phthalate metabolites and dichotomized Strength and Difficulties Questionnaire (SDQ) scores at 5 y ($n = 457$ or 458 mother–son pairs, depending of the subscale).

	Emotional symptoms		Conduct problems		Peer relationship problems		Hyperactivity–inattention problems		Prosocial behavior		Externalizing behavior		Internalizing behavior	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Phenols														
∑ Dichlorophenols	0.99	(0.87, 1.12)	0.94	(0.80, 1.10)	0.94	(0.79, 1.11)	1.10	(0.97, 1.24)	1.01	(0.87, 1.18)	1.05	(0.93, 1.18)	0.94	(0.83, 1.07)
Bisphenol A	1.04	(0.80, 1.36)	1.04	(0.76, 1.41)	1.10	(0.80, 1.50)	1.40	(1.08, 1.82)**	1.09	(0.80, 1.47)	1.20	(0.93, 1.54)	1.00	(0.96, 1.10)
Benzophenone-3	0.93	(0.82, 1.05)	1.00	(0.87, 1.16)	0.99	(0.86, 1.14)	1.05	(0.93, 1.19)	1.05	(0.91, 1.20)	1.06	(0.95, 1.18)	0.97	(0.95, 1.01)
Triclosan	1.08	(1.00, 1.18)*	1.06	(0.96, 1.17)	1.10	(0.99, 1.22)*	1.01	(0.93, 1.09)	1.00	(0.91, 1.09)	1.00	(0.93, 1.08)	1.07	(0.99, 1.03)
∑ Parabens	0.95	(0.84, 1.08)	0.96	(0.82, 1.11)	1.01	(0.87, 1.18)	0.98	(0.86, 1.12)	0.97	(0.84, 1.13)	1.01	(0.89, 1.14)	0.96	(0.96, 1.02)
Phthalates														
MEP	1.16	(0.97, 1.39)*	1.13	(0.92, 1.38)	1.02	(0.82, 1.27)	1.05	(0.87, 1.27)	0.79	(0.63, 1.00)**	1.08	(0.91, 1.29)	0.93	(0.95, 1.04)
MnBP	1.02	(0.85, 1.23)	1.06	(0.85, 1.31)	1.24	(1.01, 1.52)**	1.03	(0.85, 1.25)	0.87	(0.68, 1.10)	1.04	(0.86, 1.25)	1.14	(0.97, 1.07)
MiBP	1.01	(0.79, 1.29)	1.02	(0.77, 1.35)	1.05	(0.79, 1.41)	0.95	(0.74, 1.23)	1.02	(0.75, 1.38)	1.00	(0.79, 1.27)	0.97	(0.92, 1.05)
MCPP	1.01	(0.79, 1.29)	1.07	(0.81, 1.43)	1.20	(0.91, 1.58)	0.98	(0.75, 1.27)	0.86	(0.63, 1.17)	1.04	(0.81, 1.33)	1.16	(0.95, 1.08)
MBzP	1.06	(0.87, 1.29)	1.02	(0.81, 1.29)	0.96	(0.75, 1.22)	1.02	(0.83, 1.25)	0.79	(0.61, 1.03)*	0.91	(0.75, 1.12)	1.04	(0.97, 1.08)
MCOP	1.15	(0.91, 1.45)	0.93	(0.70, 1.23)	1.03	(0.78, 1.36)	1.23	(0.97, 1.56)	0.88	(0.66, 1.17)	1.03	(0.82, 1.30)	1.09	(0.96, 1.09)
MCNP	1.01	(0.81, 1.25)	0.90	(0.68, 1.18)	0.99	(0.76, 1.28)	1.02	(0.82, 1.28)	1.06	(0.84, 1.35)	1.00	(0.80, 1.24)	1.04	(0.98, 1.09)
∑ DEHP	1.08	(0.85, 1.36)	0.99	(0.74, 1.31)	1.18	(0.90, 1.55)	1.07	(0.84, 1.36)	0.79	(0.59, 1.07)	1.05	(0.83, 1.32)	1.15	(0.95, 1.08)

Note: CI, confidence interval; ∑DEHP, molecular sum of di(2-ethylhexyl) phthalate metabolites; ∑dichlorophenols, molecular sum of 2,4 and 2,5-dichlorophenols; MBzP, monobenzyl phthalate; MCNP, monocarboxynonyl phthalate; MCOP, monocarboxyoctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-*n*-butyl phthalate; OR, odds ratio; ∑parabens, molecular sum of methyl, ethyl, propyl, and butyl parabens. Associations adjusted for recruitment center, maternal age, parity, parental education, breastfeeding duration, household income, smoking status, maternal psychological difficulties during pregnancy, and child age at assessment. IRRs are reported for a doubling in biomarkers concentrations.
*$p \leq 0.10$; **$p \leq 0.05$.

(Braun et al. 2011) or null (Evans et al. 2014; Harley et al. 2013) associations with this subscale. Interpretation of the human literature on BPA should be done keeping in mind that BPA is one of the biomarkers with the highest within-subject variability [with intraclass coefficients of correlation of 0.1–0.2 being typically reported during pregnancy (Braun et al. 2012; Philippat et al. 2013)], limiting the power of studies relying on one spot urine sample to assess exposure, as was the case of most previous studies. Despite this limitation, most of the published studies (including ours) reported an association with one or several behavioral scores among boys (Table S11), suggesting that BPA may affect some aspects of behavior among boys. This is supported by experimental studies on laboratory animals that have also reported associations between perinatal exposure to BPA and behavior (Anderson et al. 2013; Ishido et al. 2011; Komada et al. 2014; Nakagami et al. 2009) and by *in vitro* studies that suggested that BPA can interact with some pathways that are crucial for brain development. BPA can indeed bind with estrogen and androgen receptors as well as interact with thyroid hormone pathways [reviewed by Mustieles et al. (2015)].

In our population, triclosan, a biocide used in some toothpastes, antibacterial soaps, and detergents, tended to be positively associated with the externalizing behavior score as well as with the emotional symptom and conduct problems scores at 3 y. When SDQ scores were dichotomized, associations with the emotional symptom score was also observed at 5 y. To our knowledge, this is the first study investigating triclosan potential effect on child neurodevelopment. Both *in vitro* studies and studies in rodents suggested that triclosan can affect pathways involved in the development of the nervous system, such as the thyroid hormone pathway (Paul et al. 2010, 2012). In humans, a cross-sectional study reported increased total triiodothyronine concentrations in association with increased triclosan concentrations among adolescents (Koeppe et al. 2013). Other mechanisms whereby triclosan might affect child neurodevelopment include disruption of the sex hormone homeostasis because triclosan can bind, albeit with low affinity, to both the androgen and estrogen receptors [reviewed by Witorsh (Witorsch 2014)].

Maternal urinary concentrations of ∑dichlorophenols tended to be associated with increased risk of conduct problems at 5 y. However, this association did not remain when SDQ scores were dichotomized. ∑Dichlorophenols included 2,5-dichlorophenol, a metabolite of 1,4-dichlorobenzene used in mothballs; indoor deodorizers; toilet bowl disinfectants; and 2,4-dichlorophenol, a metabolite of 2,4-dichlorophenoxyacetic acid used as intermediate in the production of some herbicides. Our study is the first to focus on these compounds in humans for behavior-specific factors. A study in which rats were exposed during pre- and postnatal life to 2,4-dichlorophenoxyacetic acid reported deleterious effect on behaviors (Bortolozzi et al. 1999) that included hyperactivity, stereotypic behavior (excessive grooming), and serotonin syndrome behaviors (forepaw tapping, sprawling of limbs, and mobility) (Bortolozzi et al. 1999). Translation to epidemiological research is difficult, given the fact that behavioral outcomes and routes of exposure differ between rats and humans.

We observed increased scores on the internalizing, relationship problems, and emotional symptoms subscales at 3 y in association with urinary concentrations of MnBP. These associations did not remain at 5 y. In a previous study among mother–child pairs from New York City, 3-y-old boys experienced more internalizing and withdrawn behaviors as well as more emotionally reactive problems in association with maternal urinary concentrations of this phthalate metabolite (Whyatt et al. 2012). Other studies among older boys (4.5 to 10 y) did not report such associations (Engel et al. 2010; Kobrosly et al. 2014; Lien et al. 2015). Experimental studies among rodents also suggested behavioral effects for this phthalate (Farzanehfar et al. 2016; Hoshi and Ohtsuka 2009; Yan et al. 2016).

In our study population, MBzP was associated with increased scores on the internalizing behaviors and relationship problems subscales at 3, but not at 5 y. Associations between MBzP and behavioral scores have been reported previously among boys, but with other subscales, including oppositional behavior and conduct problems (Kobrosly et al. 2014).

When SDQ scores were dichotomized, ∑DEHP was associated with increased risk for emotional symptoms and internalizing behavior. A few studies reported associations between DEHP biomarkers (as a sum of several metabolites or for single DEHP metabolites) and behavior in boys. These associations were seen with other subscales than those reported in our study, including

increased social, delinquent, somatic, and externalizing behavior subscores (Kobrosly et al. 2014; Lien et al. 2015). However, these two previous studies examined behavior at older age (6 to 10 y old) and had relatively low sample size ($n < 80$ for boys). Among studies of bigger sample size, one reported no association between prenatal exposure to DEHP and behavior at 3 y (Whyatt et al. 2012), while the other reported better social competence and lower hyperactivity–inattention scores at 7 y in association with DEHP biomarkers (Gascon et al. 2015). Phthalates can disrupt the thyroid and sex hormone homeostasis and calcium signaling, and can alter brain's lipid profile [reviewed by Miodovnik et al. (2014)]. They are also weak agonists of the aryl hydrocarbon (Krüger et al. 2008) and peroxisome proliferator-activated receptors (Miodovnik et al. 2014) involved in numerous developmental pathways.

Four biomarkers (benzophenone-3, $\sum$parabens, MiBP, MCPP) were associated with lower SDQ scores, suggesting improved behaviors. When SDQ scores were dichotomized, only the associations between MCPP and the prosocial behavior score at 5 y and the hyperactivity–inattention scores at 3 y remained. Previous studies that assessed this phthalate in maternal urine did not report any association with hyperactivity–inattention among boys (Engel et al. 2010; Gascon et al. 2015; Lien et al. 2015). Regarding parabens and benzophenone-3, this is, to our knowledge, the first epidemiological study that looked at their human behavioral effects, which makes it difficult to discuss the plausibility of our associations with lower SDQ scores. However, previous studies in rats exposed to parabens pre- and postnatally (via lactation) reported increased anxiety-like behavior (Kawaguchi et al. 2009) and autism-like symptoms (Ali and Elgoly 2013), as well as less social interactions and learning memory (Ali and Elgoly 2013) in exposed animals compared to controls, which is not in line with our findings. This difference and the fact that the association we observed with $\sum$parabens did not remain when SDQ scores were dichotomized should lead to cautious interpretation of the association we observed that suggested that higher concentration of $\sum$parabens was associated with more prosocial behavior.

Although most studies (including ours) that examined the associations between phthalate biomarkers and child behavior in humans reported deleterious associations, the biomarkers implicated and the affected behaviors often varied across studies. This may be explained by the large heterogeneity in age, ranging from 1 to 10 y; the different instruments used to evaluate behavior; the large number of comparisons performed in each study, which usually did not correct for multiple testing; and issues related to measurement error in the exposure assessment of biomarkers with short half-lives. Exposure was assessed using only one, rarely two, urine samples per participant collected at different time points during pregnancy, which is insufficient to characterize exposure for biomarkers with high intraindividual variabilities, as reported for some phthalates and phenols (Adibi et al. 2008; Philippat et al. 2013), and is likely to lead to attenuation bias (Perrier et al. 2016). As in most previous studies, we assessed exposure during pregnancy and were missing exposure occurring during the first years of life, also a potentially crucial time point for brain development. Socioeconomic status is likely to be a strong confounder of the associations between exposure to environmental chemicals and child neurodevelopment (Bellinger 2004). We adjusted our analyses for many potential confounders, but we cannot exclude that residual confounding remained. Among 728 Spanish women for whom exposure to 81 chemicals was assessed, BPA was not highly correlated with other environmental biomarkers, while phthalate metabolites were correlated among each other and were negatively correlated with some metals, such as cadmium and copper [rho ranged between −0.3 and −0.5, (Robinson et al. 2015)]. Although correlations between exposures possibly differ across countries, this finding suggests that the associations we observed with BPA and phthalate biomarkers are unlikely to be confounded by exposure to other chemicals. In line with this finding, associations varied little after adjusting our analyses for the other phenols and phthalates biomarkers measured in the study. We relied on the SDQ, a validated and widely used questionnaire in Europe, to assess child behavior at two different time points.

Strengths of our study include the sample size, larger than those of previous studies that included 122 to 460 boys and girls and among which analyses stratified for child sex have been often performed. The fact that we focused on boys limits generalizability of our findings, but is not a source of bias, especially in the context of endocrine disruptors for which sex-specific effects have been reported previously (Casas et al. 2015; Perera et al. 2012; Roen et al. 2015). In an attempt of correcting our findings for exposure measurement error, we present in the supplemental material the effect estimates corrected using an *a posteriori* disattenuation method (Perrier et al. 2016). As expected, the corrected effect estimates were bigger (absolute values) than the corresponding uncorrected IRRs and ORs. We believe that these corrected effect estimates are relevant for the purpose of future meta-analyses that will combine studies relying on a different number of urine samples per participant to assess exposure.

Conclusion

Several phenol and phthalate biomarkers were associated with increased scores on the SDQ subscales at 3 and/or 5 y. The associations observed for BPA and MnBP were consistent with those reported previously among boys in the same age range (Evans et al. 2014; Harley et al. 2013; Perera et al. 2012; Whyatt et al. 2012) and are further supported by the animal literature. Associations observed with MBzP, triclosan, and $\sum$dichlorophenols need cautious interpretation, since they have not been observed in previous studies (MBzP), or this study is the first to explore their potential effects on child behavior (triclosan, $\sum$dichlorophenols). Harmonizing protocols across studies (including tools used to assess behavior and age at assessment) would enhance results comparability across studies. In addition, further studies that aim at looking at the potential effects of phenols and phthalates on child neurodevelopment would benefit from incorporating new approaches to improve exposure assessment, one of the main limitations of the current epidemiological literature for these biomarkers.

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